are added. No new matter has been added to the specification by these changes. Applicant respectfully requests reexamination and reconsideration of the case, as amended. Each of the rejections levied in the Office Action is addressed individually below.

I. Rejection under 35 U.S.C. § 112, first paragraph, for lack of enablement.

Claims 35-51 stand rejected under 35 USC § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Examiner states that "applicants have not enabled one to obtain the requisite isomer with a purity of 96% or greater." Applicant disagrees and reiterates the arguments of record.

Applicant further submits that the specification (at page 21, lines 12-28) teaches a procedure by which one of skill in the art can separate the L-Pro-D-boroPro from the L-Pro-L-boroPro isomer and thereby obtain the claimed invention. The Examiner has said that the claims lack enablement because the specification fails to teach separation of *cis* and *trans* isomers. However, the claimed invention is a mixture of stereoisomers having the structure recited in claim 35, "wherein at least 96% of the carbon atoms bearing boron are of the L-configuration." The claims do not require the separation of the *cis* and *trans* isomers. Accordingly, the Examiner's reliance on a purported lack of enablement of separating *cis* and *trans* isomers as a basis for rejecting the pending claims is misplaced. Withdrawal of this rejection under 35 U.S.C. § 112 is respectfully requested.

In addition, Examiner asks whether the compound designated L,L is the *cis*-isomer or the *trans*-isomer. As pointed out in a previous Response, the compound designated L,L includes both the *cis* and *trans* isomers. There is a constant interconversion of *cis* and *trans* isomers so the compound designated L,L is a mixture of the two isomers (*i.e.*, *cis* and *trans*). This interconversion of isomeric forms of boroProline-containing compounds is similar to the interconversion of cyclohexane between the chair and boat forms. As taught in any introductory course on organic chemistry, any flask of cyclohexane will contain a mixture of both the chair and boat forms of cyclohexane, and an ordinary chemist would not likely put a label on the flask reading "Cyclohexane-boat and chair forms" unless in jest. Many complex organic molecules

forms and conformations without their being explicitly mentioned. Therefore, one of ordinary skill in the art reading the specification would appreciate that there could exist various forms of Pro-boroPro but that the claimed invention is directed to the L and D isomers of boroProline regardless of the particular conformations of the molecule.

According to the Examiner, even though the specification enables separation of *cis* and *trans* isomers of a particular compound, it does not enable preparation of the spectrum of compounds that fall within the claimed invention. This basis for rejection under 112(1) is based solely on breadth of the claim scope and does not satisfy the legal standard for a proper enablement rejection on the basis of undue experimentation. In particular, the Examiner states,

"... Moreover, even if it were true that enablement exists for purifying the compounds cis-L-Ala-L-boroPro and trans-L-Ala-L-boroPro, the claims encompass an infinite number of compounds, of size ranging from two amino acids to 2 million, and of polarities that cover the entire spectrum of highly lipophilic to highly hydrophilic. Even if applicants could make the argument that the procedure is clear for this one compound (which it is not), the issue of the cis and trans isomers would have to be dealt with for many of the remaining compounds in the genus."

The Examiner has not made a *prima facie* case of non-enablement of the claimed invention; the burden remains on the Examiner to establish a *prima facie* case based upon the proper legal standards. The Examiner's attention is directed to <u>In re Wands</u>, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) and <u>Enzo Biochem., Inc. v. Calgene, Inc.</u>, 188 F.3d 1362, 52 USPQ2d 1129 (Fed. Cir. 1999), which discusses the factors to be considered in determining whether a disclosure would require undue experimentation to practice a claimed invention:

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman, [230 USPQ 546, 547 (BdPatAppInt 1986)]. They include (the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

Accordingly, the factors that <u>must</u> be considered to establish a prima facie case of nonenablement based on undue experimentation include (1) the quantity of experimentation working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breath of the claims. Ex parte Forman, 230 USPQ 546, 547 (Bd.Pat.App.Int. 1986). Each of these factors is discussed below.

The quantity of experimentation required to separate the diastereomers of boroProlinecontaining compounds is relatively small and amounts to routine optimization in view of the specification teaching of an appropriate separation method (HPLC using a C₁₈ column and a two buffer system) on page 21 of the specification. The specification provides direction and guidance by providing an illustrative separation method and includes a working example on page 21 of the specification. This working example details the separation L,L and L,D Pro-boroPro by HPLC using a C₁₈ column with a two buffer system. The present invention encompasses both the realization that the purified L-boroProline-containing peptide analogs are more efficacious pharmaceutical agents than mixtures of the D and L isomers and the separation methods needed to separate the diastereomers. The <u>nature of the invention</u> relates to an improved preparation of diastereomers in which one optical isomer is present in a higher percentage than the other diastereomer. This invention is based, in part, on the realization that the L,L isomer is more biologically active than its L,D counterpart and, in part, on the discovery of an appropriate method to separate these stereoisomers. The state of the prior art was such at the time of the invention that one could easily prepare boroProline-containing peptides; however, one skilled in the art was not aware of the improved properties of the L,L isomer, nor of the means to separate the L,L from the L,D isomer at the time the invention was made. Given that the relative skill of those in the art of biochemistry and organic chemistry was relatively high at the time the invention was made, optimizing the disclosed method of separating the diastereomers of the invention would have been well within the ordinary skill of a chemist at the time the invention was made. Peptide synthesis is a predictable art; the separation of the diasteromeric peptides using the methods disclosed in the application represent routine optimization and does not amount to an unpredictable method. Although the breadth of the claims is relatively large, this factor alone cannot serve as a sole basis for rejecting claims. The claims which issued in U.S. Patent 4, 935,493 to Bachovchin et al., were based on the same basic boroProline-containing

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composition comprising a mixture of stereoisomers enriched in the compound having the L-configuration. Without the breadth of claims as written, the inventors would practically be deprived of any patent rights because the patent claim scope would not be reasonable in view of the inventor's discoveries. This result would certainly be against the public policy of protecting an inventor's exclusive rights in his invention for a limited time so as to encourage and promote the useful arts and sciences.

Examiner also contends that the specification, page 15, contains erroneous information which would confuse the skilled chemist. However, as Applicant has pointed out previously, one of ordinary skill in this art would realize after reading the specification that (1) the HPLC procedure reported on subsequent specification pages (page 21) would be useful for separating the diastereomers; and (2) there remained uncertainties about the ability of conventional silica gel chromatography to separate the diastereomers. One of ordinary skill in the art would conclude, in reading the HPLC method on page 21 (which unambiguously asserts the utility of the HPLC C₁₈ method for separating the diastereomers), that this HPLC method is useful for separating the diastereomers.

In summary, the procedure on page 21 of the specification unambiguously teaches the separation of L,L and L,D Pro-boroPro using the disclosed HPLC method. The composition claims are directed to a mixture enriched in the L,L diastereomer; therefore, the claims are enabled even though the purified diastereomers may include the *cis* and *trans* forms of Pro-boroPro. One of ordinary skill in the art following the procedure on page 21 will isolate the L,L-isomer including both *cis* and *trans* isomers as claimed. Since the specification teaches one of ordinary skill in the art how to make and use the claimed invention, Applicant respectfully requests that the rejection be removed.

The Examiner has failed to establish a prima facie case of non-enablement due to undue experimentation, at least because he failed to consider each of the eight factors which the Foreman and Wands courts have held <u>must</u> be considered to reach a conclusion regarding enablement of a claimed invention. For this additional reason, Applicants respectfully request withdraw of the rejection of claims under 35 U.S.C. 112(1).

II. Rejection under 35 U.S.C. § 112, first paragraph, for lack of written description.

Claims 35-51 have been rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Examiner contends that there is no support in the specification for stereochemical purities of 96%, 97%, 98%, and 99% with respect to the carbon atom bearing boron. Applicant respectfully disagrees; however, in order to further prosecution of the Application, Applicant has canceled claims 37, 38, 44, and 45, which recite purities of 97% or 98%. Applicant submits that there is adequate written description support for 96% and 99% stereochemical purity. Reconsideration and withdrawal of the rejection of the pending claims under 35 U.S.C. § 112 is respectfully requested.

The arguments of the record are reiterated here. The Examiner raises the issue of support for the limitation, "at least 96%", but fails to make a *prima facie* case that the specification does not provide support this limitation. Instead, the Examiner relies upon unsupported assertions that the meaning of the phrase, "99-6%", in the specification is not "normal English usage"; that "the writer of the specification would have written "96-99%", if that had been intended, rather than 99-96%; and that "there appears to be agreement that "99-6%" is an obvious error, that there is no agreement about what was intended in its place or what the skilled chemist would believe was intended." Respectfully, the Examiner's opinion regarding "normal English usage" and what he believes may have been in the mind of the inventor at the time the application was written is irrelevant to the legal analysis of the sufficiency of the disclosure for satisfying 35 U.S.C. § 112(1). The only legal issue for consideration that is relevant to this rejection is whether the specification contained a description of the claimed invention so as to reasonably convey to one skilled in the art, *i.e.*, a skilled chemist, that the inventor had possession of the claimed invention at the time the application was filed. "99-6%" would reasonably convey 99% to 96% to a skilled chemist.

Applicant also objects to the presentation of this written description rejection—nearly four years after the amendment was introduced. The issues which now have been raised as a basis for the rejection of claims under section 112(1) were ones which could have been raised by

compounds bearing boron are of the L-configuration" was present in USSN 08/950,452 claims 35 and 42 as amended on September 4, 1998. In fact, as early as June 24, 1999 (office action mailing date), Examiner Lukton *recommended* that applicant consider new claim 52 to further the discussion of allowable subject matter (emphasis added):

52. A method of obtaining a mixture consisting of two or more stereoisomers of formula I:

[formula omitted]

said method comprising the step of eluting a mixture of stereoisomers according to formula I through a C18 chromatographic matrix, whereby in the resulting mixture at least 96% of the carbon atoms bearing boron are of the L-configuration.

Certainly, if the Examiner recommended using the language appearing in bold and underlined in claim 52, he must have considered such language supported by the specification at the time the recommendation was made.

In the interval since the Examiner recommended new claim 52, additional Office Actions have issued; however, not until *March 2001* did the Examiner raise an objection to the language relating to "at least 96% of the carbon atoms bearing boron are of the L-configuration." In summary, three Office Actions have issued in the pending application since the limitation "at least 96%..." was introduced into the claims; however, written description was *not* identified as a basis for rejection until the fourth Office Action-more than two years after the limitation had been introduced. Applicant is entitled to timely prosecution of this application. Certainly, if the teaching of the specification were as confusing as characterized by the Examiner, this would have been raised as an issue early in prosecution and the Examiner would not have included this limitation in his proposed claim 52.

Reconsideration and withdrawal of the rejection of claims 35-51 under 35 U.S.C. § 112(1) is respectfully requested.

III. Rejection under 35 U.S.C. § 112, second paragraph, as being indefinite.

Claims 35-51 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. In particular, the Usersian Charles and Charles are the Charles and Charles and Charles are the Charles and Charles and Charles and Charles are the Charles and Charles and Charles and Charles are the Charles and Charles and Charles are the Charles and Charles and Charles are the Charles and Charles and Charles and Charles are the Charles and Charles and Charles and Charles are the Charles and Charles and Charles are the Charles and Charles and Charles and Charles are the Charles and Charles and Charles and Charles are the Charles and Charles and Charles and Charles and Charles are the Charles and Charles and Charles and Charles and Charles are the Charles and Charles and Charles and Charles and Charles are the Charles and Charles and Charles and Charles are the Charles and Charles and Charles and Charles are the Charles and Charle

hydrolyzed" as being indefinite in claims 35 and 42. Applicant submits that amended claims 35 and 42 obviate this rejection.

IV. Rejection under 35 U.S.C. §103, as being unpatentable over the prior art.

Claims 35-51 have been rejected under 35 U.S.C. § 103, as being unpatentable over Bachovchin (*J. Biol. Chem.* 265:3738-3743, 1990) or Bachovchin *et al.* (U.S. Patent 4,935,493) or Bachovchin *et al.* (WO 89/03223) or Flentke (*Proc. Natl. Acad. Sci. USA* 88:1556, 1991). The entire basis for the rejection under 35 U.S.C. § 103 "as being unpatentable over Bachovchin (*J. Biol. Chem.* 265, 3738, 1990)" is reproduced below:

"As indicated previously, Bachovchin teaches (page 3743, col 1, paragraph 3) acquisition of the requisite isomer, but that the purity was only 95%. If the requisite isomer can be obtained with 95% purity after only one pass through a column, then surely a purity in the range of 96-99.9% could be obtained after two passes.

"In their most recent response (filed 8/17/01), applicants have made no mention of the information in the indicated paragraph on page 3743. Given this teaching, one of ordinary skill could have readily arrived at the claimed invention without any modification in procedure whatsoever, other than to pass the mixture through the column twice.

"The rejection is maintained."

The arguments of record are reiterated here. Applicant has repeatedly explained to the Examiner in writing and in person the reasons why the Bachovchin (1990) JBC reference does *not* teach or suggest a method for separating the L and D isomers and has provided the Declarations of Bachovchin to establish that the Bachovchin (1990) reference does *not* teach a method to separate these isomers. Applicant believed this issue to have been finally resolved following the interview at the USPTO when the Examiner correctly summarized the evidence of record and Applicant's related arguments in the Interview Summary (emphasis added):

"Applicant argued that separation of the "D" & "L" isomers is not a straight forward matter & that the assertion of such separation in Bachovchin (1990) was incorrect. Accordingly, the D/L separation is "unexpected." The Examiner stipulated that the evidence presented indicates that the assertion in Bachovchin JBC 1990 of such separation was incorrect."

The Bachovchin Declaration evidences that the Bachovchin (1990) reference does not teach a separation of the D and L isomers. Accordingly, repeatedly using the procedure of Bachovchin (1990) by passing a sample through the disclosed column multiple times also will not result in the separation of the D and L isomers. Applicant respectfully requests closure on this issue and withdrawal of the rejection of claims under 35 U.S.C. § 103 as obvious in view of the Bachovchin (1990) reference.

Claims 35-51 are also rejected under 35 U.S.C. § 103 "as being unpatentable over Bachovchin (USP 4,935,493) or Bachovchin (WO 89/03223) or Flentke (*Proc. Natl. Acad. Sci.* 88, 1556, 1991)." The Examiner apparently misunderstands the arguments raised in response to the prior Office Action. The arguments of record are reiterated here. The Examiner is encouraged to review Applicant's prior response and consider the following additional arguments. In particular, Examiner has either misunderstood or misrepresented the statements made by the Applicant in the last Response file August 15, 2001. Applicant did not argue that thin layer chromatography or fractional crystallization provide better resolution than HPLC. Applicant only mentioned these other separation techniques as illustrations of other techniques available to an organic chemist trying to separate two stereoisomers. Applicant did not suggest that TLC or fractional crystallization is better than HPLC.

In summary, the Examiner asserts that the claimed invention is obvious because:

- A. A skilled chemist would have been motivated to select the L-isomer over the D-isomer because, "... given that there are only two isomers, they are both obvious; moreover, L-isomers are naturally occurring, and in the vast majority of cases, are more active than the corresponding D-isomers"; and
- B. A skilled chemist would have had a reasonable expectation of success that a C18 HPLC column would be useful for separating the isomers.

In conclusion, the Examiner asserts,

"A key point here is that the claims are not drawn to a method of purifying a compound. The claims are drawn primarily to a single pure The organic chemist of ordinary skill would have had the motivation to prepare a pure compound, and the means to achieve it."

With regard to the Examiner's first basis for this rejection, there is no motivation in the prior art to select the L-isomer over the D-isomer. The Examiner contends that there is motivation to select an L-isomer because the alternative D-isomer is "more active than the corresponding D-isomers." Respectfully, the generalized assertion that the L-isomer would have a greater biological activity than the D-isomer is an insufficient basis to motivate one skilled in the art to select these isomers over their D counterparts. The motivation for purposes of combining prior art references or modifying a primary reference for the purpose of establishing a prima facie case of obviousness must have a greater nexus to the claimed invention. Applicant can as easily assert that one skilled in the art would be motivated to select the D isomers because the D isomers would be expected to have a longer half life *in vivo* and the claimed invention is intended for *in vivo* use. In the face of such unsupported assertions, there is no basis for the Examiner to conclude that the skilled chemist would be more motivated to select one isomer over the other.

Even if one skilled in the art were motivated to separate and select the L-isomer (a point which Applicant disputes), there is no teaching or suggestion in the art as to how to accomplish this separation. Indeed, the Bachovchin (1990) reference suggests a conventional silica gel chromatographic method to effect the isomer separation; however, this method does not work. The Examiner appears to take the position that at the time this invention was made (priority to June 1995), C₁₈ HPLC would have been the principal separation method used by chemists to effect a separation of L and D isomers. The Examiner has provided no evidence to support this assertion but rather, has alleged that alternative methods to HPLC would not have been used because they were less effective. In addition, the Examiner appears to take the position that once the skilled chemist decided to use HPLC, he naturally would have selected a C₁₈ column for the separation. Again, no evidence—beyond an assertion of the wide availability of C₁₈ columns—is provided to support this assertion. As discussed below, these assertions are insufficient to establish a *prima facie* case of obviousness.

The Examiner's burden that has to be met for a proper and to calculation by a torse

(CAFC) (In re Dembiczak, 50 USPQ2d 1614 (Fed.Cir. 1999)). As explained below, this burden is a heavy one; however, no valid rejection can be made over a combination of prior art without satisfying this burden.

In <u>Dembiczak</u>, the CAFC held that the Patent Office failed to establish a case of *prima* facie obviousness because there was no motivation in the art to combine the teachings of references in the manner suggested by the Patent Office Examiner without applying hindsight. According to the <u>Dembiczak</u> court (citations omitted):

"35 U.S.C. 103 bars patentability when the invention would have been obvious 'at the time that the invention was made. . . . [I]t is this phrase that guards against entry into the 'tempting but forbidden zone of hindsight,' when analyzing the patentability of claims pursuant to that section. Measuring a claimed invention against the standard established by section 103 requires the oft-difficult but critical step of casting the mind back to the time of the invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then accepted wisdom in the field. Close adherence to this methodology is especially important in the case of less technologically complex inventions, where the very ease with which the invention can be understood may prompt one to fall victim to the insidious effect of a hindsight syndrome wherein that which an inventor taught is used against its teacher.

"Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of a teaching or motivation to combine prior art references Combining prior art references without evidence of such a suggestion, teaching or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability—the essence of hindsight

"[E]vidence of a suggestion, teaching or motivation to combine may flow from the prior art references themselves, the knowledge of one of ordinary skill in the art, or, in some cases from the nature of the problem to be solved, . . . although 'the suggestion [for the combination] more often comes from the teachings of the pertinent references.' The range of sources available, however, does not diminish the requirement for actual evidence. That is, the showing must be clear and particular. Broad conclusory statements regarding the teaching of multiple references, standing alone, are not 'evidence'. . . . In addition to demonstrating the propriety of an obviousness analysis, particular factual findings regarding the suggestion, teaching, or motivation to combine serve a number of important purposes, including: (1) clear explication of the position adopted by the Examiner . . .; (2) identification of the factual disputes; . . . (3) facilitation of the review on appeal."

Based on the foregoing, therefore, any rejection based on a combination or modification of references must make particular findings regarding the locus of the suggestion, teaching, or motivation to combine the prior art references. It is insufficient to limit an obviousness rejection to a discussion of the ways that the multiple prior art can be combined to read on the claimed invention. A mere reference-by-reference limitation analysis fails to demonstrate how the references teach or suggest their combination to yield the claimed invention. If one cannot discern in the rejection any finding that there was a suggestion, teaching, or motivation to combine or modify the prior art references cited against the pending claims, the conclusion of obviousness cannot stand as a matter of law.

The prior art does not provide the motivation required by law to modify the references in the manner suggested by the Examiner to obtain the claimed invention. There is no teaching or suggestion in the cited art to select the L isomer over the D isomer or of the means to obtain a mixture of isomers that contains at least 96% L isomer. Indeed, there is no teaching in any of the references cited by the Examiner of separating L from D isomers for any compound. Accordingly, at the time the invention was made, there would have been no motivation to modify the cited art to further purify L isomers in the manner suggested by the Examiner. Moreover, even if one were motivated to select the L isomers, one skilled in the art would not have had the requisite expectation of success to render the claimed invention *prima facie* obvious. These deficiencies in the cited references cannot be cured by the Examiner's assertions of motivation to select the L isomers and C₁₈ HPLC. Accordingly, there is no motivation to modify any of the references as suggested by the Examiner to obtain the claimed invention.

The Examiner asserts that one of ordinary skill in the art would have been motivated to isolate the L isomer and would have had the means to do so at the time the invention was made. There is no basis in the art of record for this assertion. The mere existence of various means of separation does not establish the means to achieve the invention. If the Examiner is relying upon "common knowledge" as the basis for this assertion, he is requested to cite a reference in support of his position. (See MPEP 2144.03).

Applicant reiterates the arguments of record to the effect that an organic chemist at the time the invention was made had at his disposal a variety of purification techniques including

etc. and that in trying to separate the stereoisomers of boroProline-containing compounds (if one had been so motivated, which Applicant disputes), it would not have been obvious which of these techniques would lead to an effective separation of the stereoisomers. And even if one had been motivated to try HPLC, one of skill in the art would still not have known what type of column, what size of column, or what solvent system to use in separating the stereoisomers. There is no evidence of record to suggest that an organic chemist would have been motivated to attempt to separate the stereoisomers of the invention by HPLC using a C₁₈ column and a two buffer system or that the skilled chemist would have had an expectation of success that this method would have been successful.

The Bachovchin Declaration evidence of record explains that the Bachovchin JBC (1990) reference did not disclose or suggest the claimed invention. The Declaration relies, in part, on an assertion that the resonance (chemical shift) exhibited by a proline ring proton in the *cis* or cyclic form of an Xaa-boroPro molecule will be different from the chemical shift for its equivalent in the *trans* form of such a compound. There is no evidence of record to dispute that a particular proton in a *trans* isomer of a particular compound can be in a radically different electronic environment from its equivalent in a *cis* or cyclic isomer. Therefore, it would seem beyond dispute that such protons can and often will have radically different chemical shifts and that there is, therefore, no fundamental reason for doubting this aspect of the Bachovchin Declaration reasoning.

It is true that with respect to enantiomers the chemical shift of the protons and the splitting of the signals by spin-spin coupling remains the same regardless of the configuration (D or L) of the molecule. Therefore, the NMR spectra of two enantiomers should theoretically be superimposable. The situation, however, becomes more complicated when a molecule has more than one chiral center such as in the case of the Ala-boroPro dipeptide. Again, stereoisomers that are enantiomers are indistinguishable by NMR; however, stereoisomers that are diastereomers are distinguishable. The same proton in one diastereomer will likely be in a slightly different electronic and/or chemical environment than the same proton in another diastereomer of the same molecule. This difference in environments will result in different NMR spectra for the two different diastereomers. With respect to a mixture of diastereomers as in the case of the Ala-

the signals and multiplets rather than the clearly resolved quartets or doublets seen in the NMR spectrum of the pure L,L stereoisomer. It is these differences between the chemical shifts and splitting patterns for certain protons in the NMR spectra for L, L and L, D Ala-boroPro, which the Bachovchin Declaration references to prove that the compounds described in the Bachovchin JBC (1990) reference were in fact a mixture of the L, L and L, D isomers. From this analysis, there is no fundamental reason to question the validity of the conclusions described in the Bachovchin Declaration.

In view of the teachings of the cited art (including the Bachovchin JBC reference teaching a silica gel column chromatography that the Bachovchin Declaration evidence establishes did <u>not</u> separate the stereoisomers) and the absence of any evidence to the contrary, it would not have been obvious to modify the teachings of the cited art in the manner suggested by the Examiner because: (1) there is no *evidence* of record to support the motivation for one of ordinary skill in the art to select the L isomers; and (2) even if one were motivated to make such a selection, one of ordinary skill in the art would not have had a reasonable expectation of success that one could effectively separate L from D isomers to obtain the claimed composition.

In view of the foregoing, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims under 35 U.S.C. § 103 as obvious in view of the cited art.

Summary

In view of the forgoing arguments, Applicant respectfully submits that the present case is now in condition for allowance. A Notice to that effect is requested.

Please charge any fees that may be required for the processing of this Response, or credit any overpayments, to our Deposit Account No. 03-1721.

Respectfully submitted,

C. Hunter Baker, M.D., Ph.D.

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Date: April 25, 2002

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner For Patents, Washington, D.C. 20231 on